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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/055,711	REBAR ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,22-28,30-48 and 52-57* is/are pending in the application.

4a) Of the above claim(s) *1,3,5,23,24,33-35,38,42-48 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,22,25-28,30-32,36,37,39-41 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/3/2007 has been entered.

Receipt is acknowledged of an amendment, filed 10/3/2007, in which claims 49-51 and 58-61 were canceled, and claims 30, 42 and 56 were amended. Currently, claims 1-5, 22-28, 30-48 and 52-57 are pending.

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the replies filed on 8/3/2004 and 11/18/2004. This restriction requirement was made FINAL in the Office action mailed 2/9/2005 and reiterated in the Office action mailed 11/15/2005.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 was withdrawn in the Office action mailed 6/14/2206. The remainder of the species election requirement was maintained in the Office action mailed 6/14/2006. Thus, the species election requirement for target sequence type (DNA), where the target is located (plant cell), and functional domain type (C1 activation domain) are maintained.

Claims 1, 33, 42-48 and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 3, 5, 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-57 are under consideration.

Claim Objections

Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 22 requires the target sequence to be in a plant cell; however, claim 22 depends from claim 30, which was amended to require the target sequence to be in a plant cell in the reply filed 10/3/2007. This is a new objection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 4, 22, 30-32, 36-37, 39-41 and 56-57 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-14, 18, 25 and 27 of U.S. Patent No. 7,273,923 (hereinafter the '923 patent). This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 22, 30, 56 and 57 are drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc finger protein comprising a non-canonical zinc finger component and a recognition region of a zinc finger binding domain that is non-naturally occurring, which is engineered to bind to a target sequence in a plant cell. Instant claims 22 and 30 encompass a genus of non-canonical zinc finger domains, where the two amino-terminal zinc coordinating residues are cysteine or histidine, and the two carboxy-terminal zinc coordinating residues are cysteine or histidine, wherein at least one of the amino-terminal zinc coordinating residues is a histidine residue or at least one of the carboxy terminal zinc coordinating residues is a cysteine residue. Instant claim 56 is drawn to non-canonical zinc fingers that are CCHC or CCCH zinc fingers, and claim 57 limits the non-canonical zinc finger to CCHC. Conflicting claim 25 is drawn to an isolated polynucleotide encoding a non-naturally-occurring protein comprising a

non-canonical C_3H zinc finger and a modified, non-naturally occurring plant zinc finger protein engineered to bind a target sequence. The specification of the '923 patent defines the C_3H zinc finger as a zinc finger as comprising Cys-Cys-His-Cys (CCHC) (e.g., column 7, lines 41-51). Thus, the polynucleotide of conflicting claim 25 is a species of the genus of polynucleotides encompassed by the instant claims. In other words, instant claims 22, 30, 56 and 57 are anticipated by conflicting claim 25. Obvious variants of conflicting claim 25 include the addition of a further functional domain, including a C1 activation domain (claims 12 and 27), inclusion of the isolated polynucleotide into a vector (claim 13) and host cell (claim 14), and embodiments where the target sequence is DNA (claim 18). Accordingly, conflicting claims 12, 13, 14 and 27 render obvious instant claims 2, 4, 31, 32, 36, 37 and 39-41.

Thus, the instant claims, if allowed, would extend patent protection of the '923 patent. Further, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the rights to the '923 invention, then two different assignees would hold patent claims to the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 30 is vague and indefinite in that the metes and bounds of the term "non-naturally occurring" are unclear. The term is unclear in that it is used to describe the zinc-finger binding protein encoded by the claimed polynucleotide, and more specifically the recognition region of a zinc-finger binding domain within the protein. The structures provided in the instant specification apply equally to naturally occurring and non-naturally occurring zinc finger proteins, and there is nothing in the claim or specification to define the metes and bound of the non-naturally occurring recognition regions or zinc finger domains. It is impossible to know whether any given sequence is within the scope of the claims without knowing whether it is found in nature. Given that proteins in nature are constantly changing, there is no way to know whether any given sequence is found in nature. Accordingly, the metes and bounds of the claim are unclear.

Claims 2, 4, 22, 25-28, 31, 32, 36, 37, 39-41 and 53-55 depend from claim 30 and are thus indefinite for the same reasons applied to claim 30.

Claim 56 is vague and indefinite in that the metes and bounds of the term "non-naturally occurring" are unclear. The term is unclear in that it is used to describe the zinc-finger binding protein encoded by the claimed polynucleotide, and more specifically the recognition helix of a zinc-finger binding domain within the protein. The structures provided in the instant specification apply equally to naturally occurring and non-naturally occurring zinc finger proteins, and there is nothing in the claim or specification to define the metes and bound of the non-naturally occurring recognition helices or zinc finger domains. It is impossible to know whether any given sequence is within the scope of the claims without knowing whether it is found in nature. Given that proteins in nature are constantly changing, there is no way to know

whether any given sequence is found in nature. Accordingly, the metes and bounds of the claim are unclear.

Claim 57 depends from claim 56 and is thus indefinite for the same reasons applied to claim 56.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action mailed 1/11/2007 and has been rewritten to address the amendments to the claims in the reply filed 10/3/2007.

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-55 are drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains a beta turn comprising two amino-terminal cysteine or histidine zinc coordinating residues and an alpha helix comprising two carboxy-terminal cysteine or histidine zinc coordinating residues, where at least one of the amino-terminal zinc coordinating residues is a histidine residue or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue and wherein the recognition region of the zinc-finger binding domain protein is non-naturally occurring and is

engineered to bind to a target sequence in a plant cell. Claims 56 and 57 are drawn to an isolated polynucleotide encoding a non-naturally occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains an amino-terminal beta turn comprising two zinc coordinating cysteine residues, and a carboxy-terminal alpha helix comprising two zinc coordinating residues where one zinc coordinating residue is a cysteine and the other is a histidine, and wherein the protein comprises a non-naturally occurring recognition helix that is engineered to bind to a target sequence. Thus, the claims are drawn to a genus of compounds that is defined by secondary structure (beta turn and alpha helix), primary structure (cysteine and histidine zinc coordinating residues that differ from the canonical C2H2 consensus), and function in that they must be capable of binding to a target sequence that is a protein or nucleic acid sequence. Given the structural limitations of the claims, the primary structure must be capable of providing the information necessary to allow the protein to fold into the recited secondary structures and bind to a target protein or nucleic acid sequence.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, while the claims contain a description of a general structure drawn to the non-canonical zinc finger component containing a beta turn comprising the two amino-terminal cysteine and histidine zinc coordinating residues and an alpha helix comprising the two

carboxy-terminal cysteine and histidine zinc coordinating residues, the structure is further limited by excluding the C2H2 structure which supports the secondary structure, instead claiming a retention of the structure without use of the standard C2H2 zinc coordinating residues. In other words, what is claimed is a structure where the critical C2H2 residues, which are used to support the secondary structure, have been replaced with amino acid residues that are not C2H2 (and whatever other amino acid changes are needed to support that replacement of the zinc coordinating residue(s)). While cysteine and histidine are both known to coordinate zinc atoms in the context of properly folded zinc fingers, these critical amino acids are not predictably interchanged (Green et al. Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action). For example, Green et al teach that the conversion of the C2H2 zinc fingers of Zif268 to C4 zinc fingers allows proper folding and function of the Zif268 zinc finger domains only if the mutation is present in zinc finger 1 or 3. In contrast, mutation of zinc finger 2 abolishes binding, which is likely a result of the inability of the protein to form the necessary secondary structure (e.g. Green et al, page 89, paragraph bridging columns). Furthermore, if zinc fingers 1 and 3 were simultaneously mutated, the protein was unable to bind DNA (e.g. Green et al, page 89, paragraph bridging columns). Thus, sequences other than the zinc coordinating residues play a role in determining the secondary structure and target sequence binding of the polypeptide. A review of the specification identified multiple examples of only one general type of non-canonical zinc finger protein meeting the claim limitations: a zinc finger protein in which the zinc coordinating residues are C2HC. There does not appear to be a description of any other zinc fingers that meet the claim limitations with regard to the zinc coordinating residues and secondary structure. Furthermore, the specification does not describe a structure function

correlation for residues that support the formation of the claimed secondary structure when a zinc coordinating residue is altered. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (e.g., specific sequences) drawn to other types of non-canonical zinc fingers which retain the canonical structure using zinc coordinating residues that are neither C2H2 nor C2HC (the only structures whose sequences are specifically described), the specification does not provide adequate written description of the claimed genus which encompasses all non-canonical zinc fingers having the canonical general structure.

With regard to the recitation of "non-naturally occurring zinc finger binding protein," the specification does not describe which zinc fingers proteins are definitively non-naturally occurring because all natural proteins are not known. Further, natural proteins encompass proteins that result from mutations that naturally occur such as point mutations and chromosomal translocations. All of the proteins not previously described which are naturally occurring are simply unpredictable because, for example, such proteins encompass proteins from mutant genes. Further, some mutant genes may result from the fusion of DNA binding domains and regulatory domains to two different proteins. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (distinguishing the isolated polynucleotide molecules that encode non-natural proteins from those that encode natural proteins), the specification does not provide adequate written description of the claimed genus.

The specification envisions the engineering of zinc finger proteins to bind DNA, RNA or protein (e.g., page 6, lines 16-18). The specification envisions the modification of zinc finger proteins by methods known in the art, including those methods taught by US Patent Nos. 6,007,988 and 6,013,453 (cited on the IDS filed 4/15/2003), as well as US Patent No. 5,789,538,

WO 95/19431, WO 96/06166, and WO 98/54311 (cited on the IDS filed 5/11/2005). However, each of these references teaches the engineering of zinc finger proteins to bind to nucleic acid. There is no art of record that provides guidance with respect to the design of zinc finger proteins for binding to protein. The examples within the specification are all directed to sequences that provide recognition of a DNA target sequence (e.g., Examples; Table 3). The specification does not describe any recognition region or recognition helix that provides recognition of protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of non-canonical zinc fingers and recognition regions or helices as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In*

re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). In the instant case, the specification describes zinc finger proteins that have the C_2HC structure that bind DNA. Description of this species of zinc finger does not predict the operability of other zinc fingers such as C_4, HCH_2, CHH_2, C_2CH, and H_4. Moreover, the specification and prior art only describe alterations of the recognition region or helix of the zinc finger domain that result in binding to a DNA target sequence. Description of these sequences does not allow one to predict those changes that will result in recognition of a protein sequence.

Given the very large genus of polynucleotides encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to structures necessary to confer the claimed secondary structure and binding properties, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57.

Response to Arguments - 35 USC § 112

The rejection of claims 58-61 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 10/3/2007.

With respect to the rejection of claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Applicant's arguments filed 10/3/2007 have been fully considered but they are not persuasive.

The response asserts that Applicant is not required to reiterate what was already known, and the engineering of the recognition region of a zinc finger protein to bind to a particular target site was known at the time of filing and described in detail on page 10, lines 17-29, including various references cited therein. While these references indicate that the engineering of zinc finger proteins to bind nucleic acid target sequences was known in the art at the time the invention was made, the claims encompass the engineering of zinc finger domains to bind protein target sequences. While the specification envisions the engineering of proteins to bind DNA, RNA or protein (e.g., page 6, lines 6-18), the specification or prior art of record does not provide specific guidance as to what structural changes can be made to support the recognition of target protein sequences.

The response notes that the Board of Patent Appeals and Interferences has recently reaffirmed that the term "naturally occurring" would be understood by persons of skill in the art to mean that it exists or is found in nature (*Ex parte Dewis et al.* (2007) Appeal 2007-1610 (BPAI)). Thus, the response asserts that in the instant case, the skilled artisan would readily understand the term "non-naturally occurring" to refer to a zinc finger containing a recognition region that does not occur in nature. One of skill would understand "non-naturally occurring" to mean not found in nature. However, understanding the meaning of the term does not provide a complete description of the genus of zinc finger recognition regions that do not occur in nature. The claims do not sufficiently distinguish between naturally occurring and non-naturally occurring proteins in that the structure of any claimed zinc finger recognition helix or region may be found in nature. A complete description of all naturally occurring proteins is not provided for comparison, and sequences found in nature are constantly changing as a result of naturally-

occurring spontaneous mutations. Thus, it is impossible to know whether any given sequence is found in nature.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 102

The rejection of claims 59 and 61 under 35 U.S.C. 102(b) as being anticipated by Miesfeld et al is moot in view of Applicant's cancellation of the claims in the reply filed 10/3/2007.

The rejection of claims 58-61 under 35 U.S.C. 102(a) as being anticipated by Hori et al is moot in view of Applicant's cancellation of the claims in the reply filed 10/3/2007.

The rejection of claims 2, 4, 25-28, 30-32 and 54 under 35 U.S.C. 102(a) as being anticipated by Hori et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/3/2007. Hori et al do not teach a polynucleotide encoding a non-naturally occurring recognition helix that is engineered to bind to a target sequence.

The rejection of claims 59 and 61 under 35 U.S.C. 102(b) as being anticipated by Green et al is moot in view of Applicant's cancellation of the claims in the reply filed 10/3/2007.

The rejection of claims 2, 4, 26-28, 30-32 and 54 under 35 U.S.C. 102(b) as being anticipated by Green et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/3/2007. Green et al do not teach do not teach a polynucleotide encoding a non-naturally occurring recognition helix that is engineered to bind to a target sequence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2; see the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference). This is a new rejection.

Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Specific plant

promoter sequences disclosed by Barbas, III et al include GCG target DNA sequences (e.g., Examples 2 and 3). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach that the Zif268 protein is a useful zinc finger framework for making modifications to the zinc finger protein, where positions in the alpha-helix (-1, 3 and 6) are involved in specific base contacts (e.g., column 21, lines 8-39). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising two amino-terminal zinc coordinating cysteine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine residues.

Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C_4 motif in the first or third zinc finger (e.g. page 87, Results). In the C_4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus at least one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence

5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Green et al teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Green et al indirectly provide evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

Because both Barbas, III et al and Green et al disclose zinc finger domains capable of binding a GCG triplet nucleic acid target sequence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the GCG-binding zinc finger domain of Barbas, III et al with the C_4 CGC-binding zinc finger domain of Green et al in the context of a three finger polypeptide where the C_4 zinc finger is the first or third zinc finger or in the context of a zinc finger containing four, five or six zinc fingers, where the C_4 zinc finger is the first zinc finger, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing a GCG triplet.

Claims 2, 4, 22, 25-28, 30-32, 36, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference). This is a new rejection.

Barbas, III et al teach polynucleotides encoding zinc finger-nucleotide binding polypeptides in combination with a pharmaceutically acceptable carrier (e.g., column 2, line 66 to column 3, line 17; column 4, lines 48-65; column 7, line 56 to column 8, line 54). Barbas, III et al teach recombinant expression vectors comprising the polynucleotides, and host cells such as plant cells comprising the vectors (e.g., column 18, line 47 to column 20, line 56; column 26, lines 38-46). Barbas, III et al teach that the zinc finger binding motif (i.e., target nucleic acid sequence) can be any sequence designed by the experiment or to which the zinc finger protein binds, and the motif may be found in any DNA or RNA sequence, including regulatory sequences such as a promoter sequence (e.g., column 5, line 11 to column 6, line 62). The target nucleotide sequence may be a sequence in a plant cell, whether it is a plant nucleotide sequence or a sequence that is not naturally occurring in the cell (e.g., column 5, lines 52-65; column 7, lines 40-48; column 26, lines 38-46). Barbas, III et al teach that the encoded zinc finger protein can be a variant, mutagenized protein and/or an expanded zinc finger protein having as many as 12 zinc fingers, which will bind a sequence of up to 36 contiguous base pairs (e.g., paragraph bridging columns 4-5; column 7, lines 20-55). Barbas, III et al teach that zif268 is a zinc finger protein that can be mutagenized and/or expanded (e.g., column 7, lines 40-55). Barbas et al specifically teach variants of zif268 zinc fingers that bind to the triplets GCG, TGT, TGG, TTG, and CTG (e.g., Figure 9). Further, Barbas, III et al teach embodiments where the polynucleotides encode the zinc finger-nucleotide binding polypeptides that are transcriptional activators in plants, and thus contain an activation domain (e.g., column 26, lines 38-58).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising two amino-terminal zinc

coordinating cysteine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine residues.

Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C_4 motif in the first or third zinc finger (e.g. page 87, Results). In the C_4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus at least one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCG TGG GCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Thus, Green et al teach a non-canonical zinc finger domain that binds to the sequence GCG when it is the first or third zinc finger. Green et al teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Green et al indirectly provide evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide encoding a zinc finger-nucleotide binding polypeptide of Barbas, III et al to include the non-canonical C_4 zinc finger domain that recognizes GCG of Green et al in the context of a three finger polypeptide where the C_4 zinc finger is the first or

third zinc finger, or in the context of a zinc finger containing up to 12 zinc fingers where the C_4 zinc finger is the first zinc finger, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing a GCG triplet.

One would have been motivated to include the C_4 CGC-binding zinc finger domain of Green et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference) as applied to claims 2, 4, 22, 25-28, 30-32, 36, 39-41 and 53-55 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This is a new rejection.

The combined teachings of Barbas, III et al and Green et al are described above and applied as before.

Barbas, III et al and Green et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and

activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 25, 36 and 39-41 under 35 U.S.C. 103(a) as being unpatentable over Green et al in view of Pomerantz et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/3/2007. Green et al and Pomerantz et al do not teach a polynucleotide encoding a non-naturally occurring recognition helix that is engineered to bind to a target sequence.

The rejection of claims 22 and 37 under 35 U.S.C. 103(a) as being unpatentable over Green et al in view of Pomerantz et al and further in view of Guyer et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/3/2007. The references do not teach a polynucleotide encoding a non-naturally occurring recognition helix that is engineered to bind to a target sequence.

The rejection of claims 25, 36, 39-41 and 55 under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Barbas, III et al (US Patent No. 6,242,568) has been rewritten as a new rejection. Currently, claims 2, 4, 22, 25-28, 30-32, 36, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998). With respect to this new rejection, Applicant's arguments filed 10/3/2007 have been fully considered but they are not persuasive.

The response asserts that Green teaches away from proteins containing an engineered recognition region as claimed, and the combination of Green and Barbas, III does not result in the claimed subject matter. This is not found persuasive. The fact that Green teaches the ability of a naturally occurring recognition region to bind to its cognate target site when certain zinc coordinating residues in the backbone region was modified does not constitute a teaching away from proteins containing engineered recognition regions. The rejected claims encompass isolated polynucleotides that encode a non-naturally occurring zinc finger protein comprising a non-canonical zinc finger component and a recognition region of a zinc-finger binding domain that is non-naturally occurring and is engineered to bind to a target sequence. The claim is not limited to embodiments where the non-canonical zinc finger domain and the non-naturally occurring recognition region occur in the same zinc finger domain. Rather, the non-canonical zinc finger domain and engineered zinc finger domain may be present in separate zinc finger domains of the same zinc finger protein. Green et al teach a C_4 zinc finger domain that binds GCG when it is the first zinc finger domain or when it is the third zinc finger domain of a three finger protein. Accordingly, Green et al do not teach away from proteins that contain non-naturally occurring recognition regions in other zinc finger domains. Barbas, III et al teach it is within the skill of the art to engineer zinc finger proteins to bind to a user specified target sequence and teaches zinc finger domains where the recognition region is naturally or non-naturally occurring and designed to bind to a target nucleic acid sequence that is present in a plant cell. The combined teachings of Barbas, III et al and Green et al meet each of the limitations of the rejected claims for the reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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